Clinical and genetic analysis of patients with pancreatic neuroendocrine tumors associated with von Hippel-Lindau disease

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Background. *Patients with von Hippel-Lindau disease (VHL) may develop pancreatic neuroendocrine tumors (PNETs), which can behave in a malignant fashion. We prospectively evaluated size criteria for resection of lesions and the role of genotype/phenotype analysis of germline VHL mutations in predicting clinical course.*

Methods. *From December 1988 through December 1999 we screened 389 patients with VHL. The diagnosis of PNET was made by pathologic analysis of tissues or by radiographic appearance. Germline mutations were determined by quantitative Southern blotting, fluorescence in situ hybridization and complete gene sequencing.*

Results. *Forty-four patients with PNETs have been identified; 25 have undergone surgical resection, 5 had metastatic disease, and 14 are being monitored. No patient who has undergone resection based on tumor size criteria has developed metastases. Patients with PNETs were more likely to have missense mutations (58%), and 4 of 5 patients (80%) with metastatic disease had mutations in exon 3 compared with 18 of 39 (46%) patients without metastatic disease.*

Conclusions. *Imaging for detection and surgical resection based on size criteria have resulted in the successful management of VHL patients with PNETs. Analysis of germline mutations may help identify patients at risk for PNET and which patients may benefit from surgical intervention. (Surgery 2000;128:1022-8.)*

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PATIENTS WITH VON HIPPEL-LINDAU DISEASE (VHL), a dominantly inherited familial cancer syndrome, are at risk of developing pancreatic cysts, microcystic adenomas, and pancreatic neuroendocrine tumors (PNETs).[1-5] PNETs are detected in 12% to 17% of patients with VHL, and these tumors can behave in a malignant fashion with up to 17% of patients developing metastatic disease.[6,7] Although these neuroendocrine tumors remain a relatively uncommon cause of death, there is a growing recognition of the potential consequences of these tumors if left untreated.

We have described our initial experience with the diagnosis and management of these lesions and made recommendations regarding resection on the basis of size and location of the primary tumor.[6] Although this approach appears to have been successful thus far, it has become increasingly evident that some patients manifest a more aggressive phenotype with respect to their pancreas lesions. On the basis of this observation, we questioned whether specific germline mutations might predispose VHL patients with PNETs to a more malignant course. Previously, we conducted a similar study for patients with VHL and pheochromocytoma.[8] We now report on our prospective experience utilizing size criteria to determine when to resect lesions in the pancreas and on the potential role of genotype/phenotype analysis

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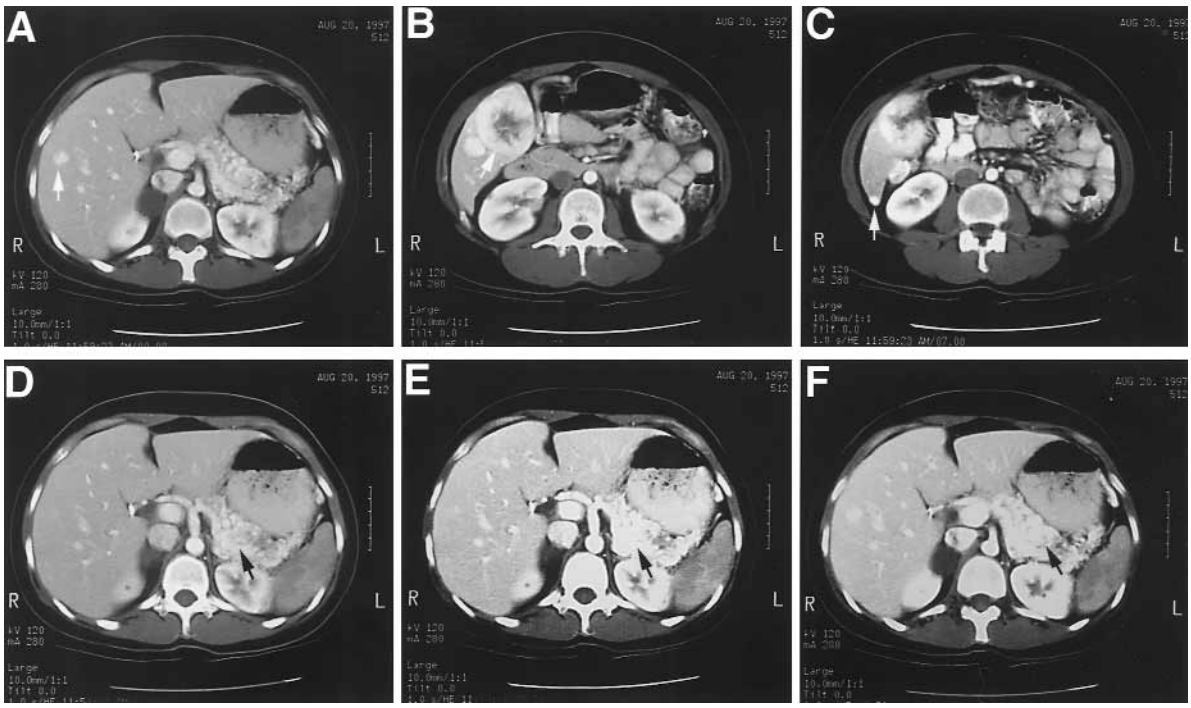

Fig 1. CT scans of a patient with a large solid lesion in the tail of the pancreas with synchronous liver metastases. **A-C** demonstrate multiple *(arrows)* hepatic metastases. **D-F** show a large infiltrating mass in the tail of the pancreas, which enhances on contrast CT.

of germline VHL gene mutations associated with these PNETs.

PATIENTS AND METHODS

We screened 389 patients with VHL between December 1988 and December 1999 at the Clinical Center, National Institutes of Healath, on a National Cancer Institute Institutional Review Board–approved protocol. The diagnosis of PNET was made either by pathologic analysis of tissue specimens or by characteristic radiographic appearance on computed tomography (CT) and magnetic resonance imaging.[1,6,9] VHL gene germline mutations were determined by quantitative Southern blotting to detect deletions of the gene, Southern blotting to detect gene rearrangements, and complete gene sequencing as described previously.[10]

The decision to perform a surgical resection of a solid tumor in the pancreas was based on criteria outlined previously.[6] Briefly, lesions were resected (1) if there was no evidence of metastatic disease, (2) if the lesion was greater than 3 cm (or greater than 2 cm if located in the pancreatic head), or (3) if the patient was undergoing a laparotomy for the management of another pathologic manifestation of VHL. Patients with lesions or clinical scenarios not fitting these criteria were followed prospectively with serial CT scans of the abdomen.

Table I. Demographics

Patients with VHL screened December 1988 to December 1999	389
Patients with PNET	44 (11%)
Male:Female	16:28
Mean age (y)	35 (range 16-68)
Number of pancreatic tumors per patient	
N = 1	30
N > 1	14
Number of patients resected	25
Number of patients with metastatic disease	5

RESULTS

Forty-four patients with PNETs have been identified. Patient demographics are outlined in Table I. The female to male ratio was 28:16 and the mean age at diagnosis was 35 years (range, 16 to 68 years). The majority of patients had single lesions (30 patients, 68%). Twenty-five patients have undergone definitive surgical resection, 5 were found to have metastatic disease at initial screening, and 14 are being prospectively followed. Fig 1

Table II. Surgical procedures and follow-up

Case No.	*Location of lesions*	*Surgery*	*Current status*	*Follow-up (m)*
1	Body/Tail	Lap-DP	NED	16
2	Head	WP	NED	12
3	Head	EN	NED	37
4	Head	EN	NED	21
5	Body/Tail	DP	NED	48
6	Head	EN	NED	40
7	Body/Tail	DP	NED	32
8	Body/Tail	DP	DOC	60
9	Head/Body/Tail	TP	NED	110
10	Head/Body	WP/EN	NED	32
11	Head	EN	NED	12
12	Body/Tail	DP	NED	74
13	Body/Tail	DP	NED	38
14	Head	EN	NED	24
15	Body/Tail	DP	NED	72
16	Head	EN	NED	16
17	Head	WP	NED	33
18	Head	WP	DOC	60
19	Head	WP	NED	12
20	Head	WP	NED	12
21	Body/Tail	Lap-DP	NED	20
22	Head	EN	NED	4
23	Head/Body/Tail	TP	NED	48
24	Head	EN	NED	15
25	Head	EN	NED	14

Lap-DP, Laparoscopic distal pancreatectomy with splenectomy; *DP*, distal pancreatectomy with splenectomy; *EN*, enucleation; *TP*, total pancreatectomy with splenectomy; *WP*, pancreaticoduodenectomy (Whipple resection); *NED*, no evidence of disease; *DOC*, died of causes other than those due to PNET.

illustrates the CT appearance of a patient with a large lesion in the tail of the pancreas and synchronous liver metastases.

The type of resection performed, length of follow-up, and current disease status are outlined for each patient in Table II. Follow-up after resection has ranged from 4 to 110 months (median, 32 months). No patient who has undergone resection of the primary tumor based on the aforementioned tumor size criteria has developed metastatic disease. A variety of surgical procedures have been performed dictated by the size and location of the lesion (Table II). Recently, we have begun to perform our distal pancreatectomies by using a laparoscopic approach.

The 44 patients with PNETs represent 36 families from a total of 188 (19%) VHL families who have had germline mutation analyses. Fig 2 is an example of a Southern blot analysis. Compared with all 188 VHL families, those with PNETs are more likely to have intragenic missense mutations (58%). Four of 5 patients (80%) with metastatic disease have mutations in exon 3 compared with 18 of 39 (46%) patients without metastatic disease. These data are presented in Table III.

DISCUSSION

Patients with VHL develop a variety of tumors involving the central nervous system and retina (hemangioblastomas and angiomas), the kidney (renal cell carcinoma), the adrenal glands (pheochromocytoma), the inner ear (endolymphatic sac tumors), the epididymis (cystadenoma), and the pancreas (neuroendocrine tumors, microcystic adenomas). The number of organ systems affected and the number of lesions present make the clinical management of these patients complex.[5,8,9,11] The lesions associated with the kidney, adrenal glands, and pancreas can be particularly worrisome because they have the potential to metastasize, resulting in life-limiting illnesses.[6-8,12]

Pancreatic lesions associated with VHL are common and can be found in 35% to 75% of patients.[2,3] The most prevalent pancreatic lesions are benign simple cysts and microcystic adenomas.[1-3] These lesions rarely present a clinical problem, with the exception of pancreatic insufficiency seen occasionally with complete cystic replacement of the pancreas.[13] Neuroendocrine tumors of the pancreas are less common and are seen in 12% to

17% of patients with VHL.[6,7] The majority of these tumors are nonfunctional and therefore are asymptomatic.[6] However, given the malignant potential of these lesions, it is important to identify those patients at risk early to maximize the potential benefits of surgical resection.

Our current strategy is to begin screening all patients with VHL for abdominal lesions at age 12 years.[9,14] With respect to the pancreas, we have found CT scanning to be the most useful for detection, with the finding of an enhancing lesion of the pancreas strongly suggestive for a neuroendocrine tumor.[6,9] Once a putative PNET has been identified on CT scan, a magnetic resonance imaging scan can be useful, with the finding of increased signal intensity on T2-weighted images being very supportive of the diagnosis.[6] With this approach we have described in this article the identification of 44 patients with PNETs. Of this group, 39 patients were candidates for resection of the primary tumor and 5 patients were found to have metastatic disease at the time of initial visceral screening.

For the 39 patients eligible for resection we applied criteria for resection based on size as we have described previously.[6] Twenty-five patients fulfilled the criteria, with lesions either being greater than 2 to 3 cm (head versus body/tail) or by virtue of the need to undergo an abdominal exploration for the resection of a kidney or adrenal lesion. The remaining 14 patients who did not fulfill resection criteria are being monitored with serial (yearly) CT scans of the abdomen. Of the 25 patients who have undergone resection, no patient has developed metastatic disease with a follow-up of 4 to 110 months (median, 32 months).

Although this strategy has been promising thus far, it is our desire to refine our recommendations and potentially identify those patients at greatest risk for developing PNETs and metastatic disease. We have observed that mutant VHL alleles are associated with distinct phenotypes.[15] This finding led us to conduct a genotype/phenotype analysis for patients with VHL and pheochromocytomas.[8] Our results suggested that VHL families with missense mutations were more likely to develop pheochromocytomas.[8] By using a similar approach, we have in the present study analyzed the data with respect to PNETs.

Our data indicate that, similar to patients with pheochromocytomas, patients with PNETs are likely to have missense mutations (58%). Furthermore, 4 of 5 patients (80%) with metastatic disease had mutations in exon 3 compared with 18 of 39 (46%) patients without metastatic disease. Exon 3 has been shown by others to be associated with pancreatic lesions in VHL.[16] Because of the small sample size, it is not possible to draw strong statistical conclusions. However, these observations may be important and will be the focus of further study.

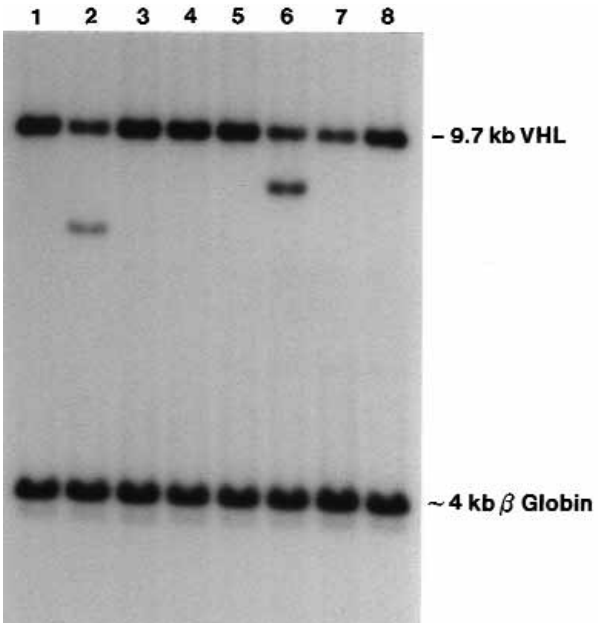

Fig 2. Southern blot analysis with VHL probe to detect germline VHL gene abnormalities in at-risk individuals. Patients whose germline abnormality is a partial deletion of the gene *(lanes 2 and 6)* reveal a less intense 9.7-kb band and an abnormally migrating band. Those samples characterized by a complete germline deletion of the VHL gene also reveal a decreased intensity of the 9.7-kb band. Reprinted from Stolle et al.[10]

There is strong evidence to support that the disease-causing germline VHL mutations are loss of function mutations, consistent with a two-hit Knudson[17] model of a tumor suppressor gene. In the pancreatic and other lesions there is loss of the second VHL allele.[1,18] In addition, when a wild-type copy of the VHL gene is put back into cell lines characterized by a mutant VHL gene, marked reduction or complete loss of tumorigenesis is observed.[19] However, we have not completely excluded the possibility that some VHL gene mutations may have a dominant-negative effect. We are currently pursuing laboratory studies to address this question.

On the basis of these findings, we conclude that an aggressive approach to imaging for detection[9] and surgical resection based on established size criteria[6] can result in the successful management of VHL patients with PNETs. The only concrete "proof" that such a strategy is "better" than, for example, observation of these malignant PNETs would come from a randomized trial of surgical

Table III. Characteristics of VHL patients with PNETs

Patient No.	*Age at diagnosis (y)*	*Sex*	*Family mutation*	*Diagnosis, no. of tumors*	*Family*	*Patients with metastases*
1	38	F	deleted 1 allele	P, 1	5955	
2	32	M	deleted 1 allele	P, 1	6001	
3	34	M	partial deletion	P, 2	3647	
4	53	M	partial deletion	R, 1	3647	
5	34	F	partial deletion	P, 1	6002	
6	53	F	partial deletion	R, 2	6003	
7	26	F	nt 393 del G, codon 137 exon 1, stop	R, 1	2656	
8	42	F	nt 393 del G, codon 137 exon 1, stop	P, 1	2656	
9	32	M	3´ deletion, part exon 2 and exon 3	P, 1	4044	
10	20	F	nt 430, C to T, Gln to stop	P, 1	2735	
11	32	F	nt 688 del A, frameshift	P, 1	1112	+
12	28	F	nt 694 C to T, Arg to stop, exon 3	P, 1	6004	
13	21	F	nt 694 C to T, Arg to stop, exon 3	R, 1	6005	
14	42	M	nt 703 C to T, Gln to stop, exon 3	P, 1	5956	
15	21	F	nt 753-756, del CGTC, missense	R, 1	1111	
16	24	F	nt 768, C to G, Tyr to stop, exon 3	P, 1	6006	
17	29	F	nt 439-441 del TTC, del Phe	P, 2	6007	
18	19	F	nt 470 C to G, Pro to Arg	R, 1	4117	
19	37	M	nt 475 T to A, Trp to Arg	R, 1	6008	
20	68	M	nt 491 G to A, Gly to Asp	R, 1	6009	
21	23	F	nt 506 A to C, Tyr to Ser	P, 2	6010	
22	31	M	nt 553 G to C, Gly to Arg	P, 1	3816	+
23	34	M	nt 553 G to C, Gly to Arg	P, 1	6011	
24	38	F	nt 594, 595 GC to TT, Leu to Phe	P, 1	3775	
25	50	F	nt 658 G to T, Ala to Ser	R, 2	6012	
26	55	F	nt 658 G to T, Ala to Ser	R, 1	6012	
27	27	F	nt 658 G to T, Ala to Ser	R, 1	6013	
28	43	F	nt 695 G to A, Arg to Gln	R, 1	6014	
29	29	M	nt 699 C to G, Cys to Trp	P, 2	3618	
30	50	M	nt 712 C to T, Arg to Trp	R, 1	3407	
31	33	M	nt 712 C to T, Arg to Trp	R, 1	3407	
32	34	F	nt 712 C to T, Arg to Trp	P, 2	2301	+
33	20	F	nt 712 C to T, Arg to Trp	P, 1	2301	+
34	43	F	nt 712 C to T, Arg to Trp	P, 3	4477	
35	20	F	nt 712 C to T, Arg to Trp	P, 3	5957	
36	27	F	nt 712 C to T, Arg to Trp	P, 3	6015	
37	46	F	nt 712 C to T, Arg to Trp	P, 1	6016	
38	41	M	nt 713 G to A, Arg to Gln	R, 1	5960	
39	39	F	nt 713 G to A, Arg to Gln	P, 1	5960	
40	31	F	nt 713 G to A, Arg to Gln	P, 1	3488	+
41	48	M	nt 713 G to A, Arg to Gln	P, 5	5069	
42	16	M	nt 713 G to A, Arg to Gln	P, 3	5069	
43	35	F	nt 454 C to T, Pro to Ser nt 775 C to G, Leu to Val	P, 4	5959	
44	39	M	nt 776, T to C, Leu to Pro	P, 2	6017	

P, Pathologic; *R*, radiologic.

therapy versus observation. However, as we and others have observed, these lesions can behave in a malignant and aggressive manner. Therefore, a more rational approach toward defining the optimal management strategy will likely result from prospective trials of organ-sparing surgery.

Analysis of germline mutations has revealed that exon 3 may represent a "hot spot" predisposing to a more aggressive phenotype. Such an analysis may help predict those patients with VHL who are at risk for developing PNET. This approach may also help to identify those patients

with PNET who may benefit from earlier surgical intervention to prevent spread of disease.

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DISCUSSION

Dr Göran Åkerström (Uppsala, Sweden). This is an interesting series of patients with very uncommon tumors. We recently had a VHL patient with a pancreatic tumor accidentally discovered during operation for bilateral pheochromocytoma. The tumor was 1 cm in size in the middle of the pancreas and was radically removed by resection of the pancreatic body and tail. Five years later a new pancreatic tumor occupying the entire pancreatic head was detected, which by fine-needle biopsy was demonstrated to be a neuroendocrine carcinoma. That is a development we are really scared of because rapidly growing neuroendocrine carcinomas are tumors with really bad prognosis. How can you be sure that an endocrine pancreatic tumor you follow without surgery is an indolent "benign" endocrine pancreatic tumor and not a neuroendocrine carcinoma?

Dr Libutti. That is an excellent question. It really gets to the heart of the issue for which we struggle with these patients. Does one operate on every patient in whom you detect a potential neuroendocrine tumor? And then, what operation do you do? In these patients with a familial cancer syndrome, the entire pancreas remains at risk as your patient clearly illustrates. This patient had a previous neuroendocrine tumor removed but developed a new neuroendocrine tumor or had one grow to a size you could detect over the period of time in follow-up. So unless one were to recommend doing total pancreatectomies on all of these patients, the issue remains that they still have tissue at risk.

It is difficult to determine or to ascribe the diagnosis of carcinoma to these lesions based on histopathology. All of these lesions are potentially malignant, and it may be that as they grow larger, the statistical probability of them metastasizing increases. We would not feel comfortable with a 3-cm lesion if we biopsied it and found that there were no characteristic features that a pathologist would call carcinoma.

So I think our best strategy at this point is to attempt to make a rational decision on operative strategy as well as to determine what the true natural history of these lesions is. In so doing we have established some criteria for who to operate on and then to very carefully follow those other patients.

Is there a risk that those other patients may develop metastatic disease? Admittedly, yes, although we have not seen in the patients whom we have screened in over 10 years any patient with a lesion smaller than 3 cm develop metastatic disease. It may just be a matter of time or we may have been lucky so far.

Dr Åkerström. I agree with your opinion that virtually all these tumors are potentially malignant. But I want to warn about a special variety that we knew from the nonfunctioning endocrine pancreatic tumors, and that is the carcinoma type. It is clearly differentiated. Do you have a mean survival time of months compared to years? These patients had to be treated with total pancreatectomies.

Dr John Chabot (New York, NY). Have you any information about genetic screening in the VHL gene in the larger population of patients who present with nonfunctional islet cell tumors? Would you make any recommendations for incidental islet cell tumors that are nonfunctional that are found outside of the VHL gene family?

Dr Libutti. We have not specifically looked at the genetics in patients with nonfunctional neuroendocrine tumors outside of VHL. Dr Warshaw's group in Boston has looked at some of these patients from the point of view of genetic germline mutations and mutations in the tumors. They found some association with chromosome 3, although not at the VHL locus.

I think it will be interesting as data are accrued from a number of centers to see whether true differences exist in the types of mutations and what the pathogenesis of these tumors is. We have not focused any efforts to date on the non-VHL nonfunctional neuroendocrine tumors.

Dr Norman Thompson (Ann Arbor, Mich). I believe this is the largest series of islet cell tumors associated with VHL to be reported.

In our experience, virtually every one of the patients whom we have had has had a concomitant lesion that required an operation such as a pheochromocytoma or renal cell carcinoma. You showed a picture with liver metastases and attributed those to the neuroendocrine tumors in the pancreas. I don't think you can say that unless you have absolutely ruled out renal cell carcinoma because they are so common in association with the neuroendocrine pancreatic tumors. Of all the cases you operated on, how many had either a nephrectomy or a pheochromocytoma excised at the same time?

Dr Libutti. We went through pains to make certain when we were calling metastatic disease in our 5 patients that it was due to a neuroendocrine tumor. You are absolutely right; many of the patients in our series had concomitant other lesions, most commonly, pheochromocytomas. It seems that the neuroendocrine tumors of the pancreas segregate with pheochromocytomas.

In the patient whose x-ray I showed, we treated that patient with a distal pancreatectomy and an isolated hepatic perfusion for her liver lesions. She is now 1 of the patients who is alive with disease. She had a very dramatic response to liver perfusion and is now 4 years out from that. We obtained multiple biopsies of the liver tumors at the time of surgery and were able to establish that those lesions were of neuroendocrine origin and not an adrenal tumor. That patient did not have adrenal disease.

With regard to the number of patients who had other lesions with VHL, most of them had adrenal lesions. Many of those underwent an adrenalectomy prior to our operation for pancreatic lesions. A few had adrenalectomy at the same time and some others subsequent to that.

Interestingly, we have only had a handful of patients, probably 5, whom we have operated on who had renal cell carcinoma. One had a single lesion in the kidney that we resected at the same operation. We acknowledge a potential problem when you have a patient with multiple primaries. One has to be careful in ascribing metastatic disease to the PNET and be certain that it is not due to one of the other lesions.